

Evidence-Based Nephrology

António Vaz Carneiro

Centre for Evidence-Based Medicine.
University of Lisbon School of Medicine. Lisbon, Portugal.

Received for publication: 18/08/2006

Accepted: 02/10/2006

■ INTRODUCTION

- How do we slow the progression of diabetic nephropathy?
- How do we prevent contrast nephropathy?
- What are the most important cardiovascular risk factors in patients with decreased renal function?

These are some of the infinite number of questions a nephrologist faces during the course of a normal day's work. Even if we multiplied these queries several times over we would still not cover a significant part of the clinical problems nephrologists all over the world face. Modern clinical practice needs answers of the highest quality if clinicians are to satisfy the ever-growing need for quality of care that patients, managers, third-party payers, politicians and professional organizations demand of us.

The classic approach to getting high quality information – i.e. calling upon one's experience, replicating what was learned in medical school or asking experts (if they can be reached in time) – has been shown to possess biases that impact on its clinical usefulness¹. Indeed, a new landscape has opened up that increases the level of accountability of the individual doctor towards society at large and patients individually, making the practice of medicine more complex and the need for high quality relevant clinical information more pressing.

Faced with these constraints, what should the individual nephrologist do?

■ THE ROLE OF EVIDENCE IN CLINICAL DECISIONS AND THE DEFINITION OF EVIDENCE-BASED NEPHROLOGY

Modern nephrology practice is characterised by constant change. Regardless of his/her practical field (clinical, laboratory or imaging), every nephrologist experiences gaps in his/her knowledge which are common to all medical specialities. New advances in diagnosis and treatment come thick and fast, creating difficulties of practice and knowledge for those with the medical responsibility for caring for patients, so how can a doctor control innovation and information, in order to bring about changes in his/her practice for the benefit of his/her patients?²

The information the clinician needs can be classified under four main headings:

- answers to queries and problems emerging during clinical work³
- updating of knowledge²
- support for teaching and learning activities⁴ and
- basic or clinical research⁵.

Each one of these roles demands specific information whose urgency and importance can vary, but which implies searching out, selecting and applying evidence found in bibliographic medical databases.

Scientific evidence should be the main source of information for the modern clinician, especially as a basis for medical decision making. Indeed, we think that there are ethical obligations to practice scien-

tific medicine⁶ and the modern version of this is called Evidence-Based Medicine (EBM)¹.

But what is EBM? Evidence based medicine is "...the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"⁷. EBM practice blends the clinician's individual expertise with external scientific best evidence generated by clinical research. Individual expertise should be understood as proficiency as well as the judgement and decision-making capabilities used by clinicians in clinical practice. This may be shown by an additional capacity for diagnosis, selection of individual patient therapeutic schemes which encompass patient choice, keeping a balanced professional relationship with other professionals and with the health system in general. External scientific best evidence usually arises from clinical research (or, at times, from basic research), and is aimed at the patient (determination of diagnostic test characteristics, effectiveness of therapeutic schemes or even prognostic determination, for example). New evidence will, naturally, replace traditional clinical decision based on authority, introducing new information that will help diagnose and treat situations found in daily clinical practice with exactitude and efficiently⁸. When applied to kidney diseases, EBM is called Evidence-Based Nephrology (EBN).

■ THE PRACTICE OF EVIDENCE-BASED NEPHROLOGY

When faced with a 32-year man, suffering from IgA nephropathy (IgAN), a number of questions arise that need fast and specific answers: Why do we treat patients with IgA nephropathy? How do we decide which patients should be treated? What are the general treatment guidelines for all IgA patients? What is the role of specific therapy such as fish oils, tonsillectomy, and immunosuppression in the treatment of patient with IgAN?

Several possibilities are open to the nephrologist in search of scientific evidence on which his/her final

options will be based: a) to ask a colleague, and accept his/her counsel; b) to consult a classic textbook; c) look up a personal article from his/her private files; or d) to search a medical database, select the evidence based upon a predefined search strategy, critically appraise it based on previously defined methodological criteria (see table I for a clinical trial), and summarise it.

Table I

Guidelines for critical appraisal of a clinical trial

Is the study valid?
Was the diagnosis of disease well defined?
Were the inclusion and exclusion criteria well defined?
Were the patients randomized?
Was randomization concealed?
Were the patients treated within the groups into which they were initially distributed (intention-to-treat)?
Was the randomization method explained?
Was the sample size calculated?
Were the two (or more) groups of patients similar in their known prognostic factors?
Were the patients treated the same way at baseline?
Was the study simple, double or triple blinded?
Was the drop-out rate 20% or less?
Are the results important?
What was the treatment benefit (RRR, ARR, NNT)?
What was the precision of the results (CI)?
Is the benefit clinically important?
Are the results applicable?
Are the study patients similar to ours?
Were all the clinically important results included?
Do the benefits of treatment outweigh the risks and cost?

Definitions:

RRR – Relative risk reduction (constitutes an estimate of the proportion of baseline risk that is reduced by the therapy; it is calculated by dividing the absolute risk reduction by the absolute risk in the control group)

ARR – Absolute risk reduction (it is the difference in the absolute risk – percentage or proportion of patients with an outcome – in the exposed vs. the unexposed groups, used in a beneficial intervention)

NNT – Number needed to treat (it is the number of patients who need to be treated over a specific period of time to prevent one bad outcome; it is the inverse of the absolute risk reduction)

CI – Confidence interval (it is the range of values within which it is probable that the true value lies for the total population of patients from whom the study patients – sample – were selected)

This last option is obviously very complex, so the physician could make a search of secondary evidence* on which to base his/her options. This is a new approach to medical practice, based on some essential concepts. Firstly, while the clinical expertise of

* Secondary evidence is the one based on primary studies addressing for example a therapeutic question, duly combined and analysed under the format of systematic reviews, meta-analysis or clinical practice guidelines.

the individual doctor is a valuable tool in daily practice, it is insufficient. Secondly, the collection of facts related to diagnostic, prognostic or therapeutic aspects obtained from systematised clinical studies and trials is the most valid evidence. Finally, we have evidence rules needed to make a correct evaluation and interpretation of biomedical literature – such as in aetiology, prognostic, diagnostic, therapeutic and iatrogenic studies and articles – available. The answer to the above question could be found in a recent systematic review where all the treatment options of the IgA nephropathy are addressed and criticised⁹.

What of the questions we posed in the beginning? A brief search allowed us to select and appraise several recent papers with an excellent methodological quality that can be used as a base for our decisions:

- *How do we slow the progression of diabetic nephropathy?*

A recent published clinical trial¹⁰ compared the effectiveness of verapamil and trandolapril in preventing the development of microalbuminuria in 1204 patients with type 2 diabetes mellitus, hypertension, and normal urinary albumin excretion rates. There were 4 treatment arms: trandolapril (2 mg/d) alone, sustained-release verapamil (180 mg/d) alone, combination therapy with trandolapril (2 mg/d) and sustained-release verapamil (180 mg/d), or placebo. Patients were followed for 3 years or until persistent microalbuminuria (defined as an overnight urinary albumin excretion rate of 20 µg/min at 2 consecutive visits) developed (median, 3.6 years). Persistent microalbuminuria developed less frequently in patients who received combination therapy with trandolapril and verapamil (5.7%) than in patients who received placebo (10.0%), and more frequently in patients receiving verapamil therapy (11.9%) than in those receiving trandolapril therapy (6.0%). The incidence of microalbuminuria was similar in the verapamil and placebo groups. Blood pressure measurements were lower in the groups receiving trandolapril therapy (either alone or in combination with verapamil) than in the group receiving placebo, but there was no difference in blood pressure between the verapamil group and the placebo group. The incidence of adverse events was similar in the 4 groups. In summary, therapy with trandolapril plus verapamil or trandolapril alone decreased the incidence of microalbuminuria in patients with type 2 diabetes, hypertension, and normal urinary albumin excretion rates.

- *How do we prevent contrast nephropathy?*

Existing strategies for preventing contrast nephropathy in hospitalized patients include pre-treatment with 0.45% saline or with N-acetylcysteine, although the effects of the latter vary with setting, patient population, and procedure. A randomised controlled trial compared the prophylactic effect of a sodium chloride infusion with that of a sodium bicarbonate infusion¹¹. Patients (n=119) were included if they had baseline serum creatinine levels of 97 µmol/L or higher and were scheduled to undergo cardiac catheterization (the most frequent procedure), computed tomography, diagnostic or therapeutic angiography, or portal systemic shunt placement requiring contrast administration. Patients were randomly assigned to receive a bolus infusion (154 mmol/L in dextrose and water) of sodium bicarbonate or sodium chloride, 3 mL/kg of body weight, 1 hour before contrast administration and an infusion of the same fluid, 1 mL/kg per hour, for 6 hours after contrast administration. Serum creatinine level was measured at baseline and 1 and 2 days after contrast administration. The primary outcome measure was development of contrast nephropathy, defined as an increase of 25% or more in baseline serum creatinine levels. Of the total 119 patients enrolled, 59 received sodium chloride, and 60 received sodium bicarbonate. Of the 59 patients receiving sodium chloride infusions, 8 (13.6%) developed contrast nephropathy compared with 1 of 60 (1.7%) receiving sodium bicarbonate infusions (ARR=11.9% CI, 2.6 to 21.2 %, P≤0.020). Estimated glomerular filtration rate (GFR) increased by 8.5% in patients receiving sodium bicarbonate, whereas estimated GFR decreased by 0.1% in those receiving sodium chloride infusions (P≤0.020). In summary, hydration with sodium bicarbonate was more effective than sodium chloride in preventing radio contrast-induced acute renal failure.

- *What are the most important cardiovascular risk factors in patients with decreased renal function?*

End-stage renal disease is known to substantially increase a patient's risk of death from cardiovascular disease. The authors of this study¹¹ examined the association between estimated GFR and risk of death, cardiovascular events, and hospitalization. It included all adult members of Kaiser Permanente of Northern California (1 120 295) whose kidney function had been determined by one or more serum creatinine level measurements between 1 January 1996 and 31 Decem-

ber 2000. The patients (mean age, 52 years; 55% women) had not previously required dialysis or transplantation for end-stage renal disease and were therefore eligible to participate. The authors estimated each patient's GFR by using the Modification of Diet in Renal Disease (MDRD) equation. Median follow-up was 2.84 years (3 132 192 person-years). The investigators found that patients with a lower estimated GFR were more likely to be older and in an ethnic minority group. These individuals also had a higher prevalence of previous hospitalizations and pre-existing cardiovascular disease, proteinuria, diabetes, hypertension, hypoalbuminemia, and other comorbid conditions. During the observation period, 0.28% of patients began maintenance dialysis and 0.03% underwent renal transplantation. There were 51 424 deaths, 138 291 cardiovascular events, and 554 651 hospitalizations. The adjusted risk for cardiovascular events and hospitalizations increased in a stepwise fashion in participants with lower estimated GFRs and was more than 3 times greater in patients with an estimated GFR less than 15 mL/min per 1.73 m² than in those whose GFR was greater than 60 mL/min per 1.73 m². The presence of proteinuria was also an independent predictor of death, cardiovascular events, and hospitalization.

CONCLUSIONS

The practice of evidence based nephrology requires self-sufficient clinicians who search for answers to patient's questions using less traditional ways to access knowledge. Nephrologists practicing EBN will have to develop individual skill in searching for and selecting the medical literature, with a subsequent application of formal rules for validating that information¹². EBN decreases the importance of intuition and non-systematic clinical experience, as well as pathophysiological reasoning as the unique basis for clinical practice. The current practice of medicine puts a high level of importance on traditional scientific authority, not only as the individual expert opinion, but also from consensus protocols in obtaining the answers to questions occurring in everyday clinical practice.

Evidence-Based Nephrology forces the clinician to understand the evidence and to understand rules for critically appraising it, in order to correctly interpret the literature on causality, diagnosis, treatment and

prognosis. This implies that the clinician is in constant search of original literature, accepting the occasional lack of evidence capable of supporting his/her everyday decisions. He/she also has to accept the uncertainty that medical practice inevitably brings to the surface^{13,14}. One can say that this is not a new approach at all, since doctors usually identify clinical questions and search for their answers via scientific literature queries. The difference consists in what EBM stands for, which is explicit analysis of evidence allowing searches to become simpler and easier, benefiting not only individual doctors but also medical groups. Obviously, the underlying idea of EBM is that doctors who understand and practice EBM will be able to provide better care for their patients.

Conflict of interest statement. None declared.

References

- 1 Mayer D. Essential evidence-based medicine. 1st ed. Cambridge: Cambridge University Press; 2004.
- 2 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology. 2 ed. Boston: Little, Brown and Company; 1991.
- 3 Covell DG, Uman GC, Manning PR. Information needs in office practice: are they being met? *Ann Int Med* 1985;103:596-599.
- 4 Williamson JW, German PS, Weiss R, Skinner EA, Bowes FI. Health science information management and continuing education of physicians. *Ann Int Med* 1989;110:151-160.
- 5 Freemantle N, Mason JM, Haines A, Eccles MP. CONSORT: an important step toward evidence-based health care. *Ann Int Med* 1997;126:81-82.
- 6 Goodman KW. Ethics and evidence-based medicine. 1st ed. Cambridge: Cambridge University Press; 2003.
- 7 Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312:71-72.
- 8 Hayes RB, Devereux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. *ACP J Club* 2002; 136:A-11-A-13.
- 9 Appel GA, Waldman M. The IgA nephropathy treatment dilemma. *Kidney Int* 2006;69:1939-1944.
- 10 Ruggenenti P, Fassì A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2006;351:1941-1951.
- 11 Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-1305.
- 12 Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-2425
- 13 Carneiro AV. A prática clínica é arriscada e incerta. 1ª parte. *Revista da Ordem dos Médicos* 2002; 18:32-36.
- 14 Carneiro AV. A prática clínica é arriscada e incerta. 2ª parte. *Revista da Ordem dos Médicos* 2002; 31:18-21.

Correspondence to:

Prof. A. Vaz Carneiro
Centre for Evidence-Based Medicine
University of Lisbon School of Medicine
Av. Prof. Egas Moniz
1649-028 Lisboa
Portugal